

# Urinary Tract Infections in Children

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## Part III—Treatment of Ureterovesical Reflux

DUNCAN E. GOVAN, MD, PhD  
WILLIAM R. FAIR, MD  
GERALD W. FRIEDLAND, MD  
ROY A. FILLY, MD  
Stanford

THE PURPOSE of this article, part III of a trilogy, is to review the present status of a group of children with ureterovesical reflux who were observed at Stanford Medical Center and to discuss some general thoughts about the management of these children. Specifically, we will present and discuss the following:

- The incidence and type of infections in a group of children with reflux followed two to ten years.
- The results, infection history and complications of antireflux operations in a group of 61 children.
- The infection history in a group of 73 children with reflux who were treated medically.

Throughout this article the type of reflux to which we are referring is that attributable to a defective ureterovesical junction.<sup>1,2</sup>

This is Part III of a paper in three parts.

From the Department of Surgery, Division of Urology, and the Department of Radiology, Division of Diagnostic Radiology, Stanford University Medical Center, Stanford.

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Dr. Filly is an Academic Trainee in Diagnostic Radiology, Grant No. GM 1707, National Institute of General Medical Sciences, National Institutes of Health, USPHS.

Reprint requests to: D. E. Govan, MD, Division of Urology, Department of Surgery, Stanford University Medical Center, Stanford, CA 94305.

*Of 134 girls with demonstrable ureterovesical reflux, 61 (105 ureters) had the reflux surgically corrected with an overall surgical cure rate of 97 percent. In the remaining 73 children (112 ureters), the reflux was treated conservatively with medical management alone. During the follow-up period no significant differences were demonstrated in the overall incidence of urinary tract infection; two years following corrective operation or medical treatment more than 50 percent of both medically and surgically treated children were still experiencing infections. A pronounced decrease, however, occurred in the incidence of clinical pyelonephritis among the surgically treated group. Following correction of reflux, the incidence of pyelonephritis was similar in both medically and surgically treated cases and was approximately the same as that found in a comparable group of children without reflux.*

*In approximately two-thirds of refluxing renal units in which there was evidence of clubbing and scarring before medical or surgical therapy, deterioration progressed during the follow-up period. In most of these cases infection control was felt to be inadequate with episodes of clinical pyelonephritis occurring during the period of medical management, or, in the surgically treated group, occurring just before corrective operation and the scar appearing within two years after operation.*

*The majority of renal units in which calyceal clubbing and parenchymal scarring was present had the most severe grades of reflux.*

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### Material and Methods

**Patient categories.** This study concerns the investigation, treatment and follow-up of 134 girls with demonstrable ureteral reflux; 61 of them (105 ureters) subsequently had ureteral reimplantation while 73 of them (112 ureters) received medical treatment only (Table 1).

The diagnosis of infection was based in all instances on a positive urine culture, as described in detail previously.<sup>3</sup>

**Radiological techniques.** All patients had excretory urograms and voiding cystourethrograms.<sup>4</sup> In many instances the excretory urograms were performed elsewhere but, in general, our Radiology Department did the cystourethrograms.

**Operation technique.** Originally we employed the Hutch modification of his original reimplantation technique, then progressed to the Hutch advancement reimplant;<sup>5</sup> but because of an unacceptably high incidence of failure to correct the reflux, we adopted the Politano-Leadbetter approach.<sup>6</sup> Currently we use a variation of the original Politano-Leadbetter technique in exposing the ureter outside the bladder as well as enucleating it from within. The ureter is re-joined under direct vision, using the Politano-Leadbetter tunneling principle. In second procedures following initial failure or when the ureter had become severely dilated, we cut across the ureter flush with the outside of the bladder and carried out re-anastomosis by the Politano-Leadbetter technique. If the ureter was severely dilated we tapered the distal one-third before reimplanting it.

### Treatment and Results

The grade of reflux varied in the two groups; the children who were treated surgically usually were those who had the more severe reflux (Table 2).

#### Results of Operation

**Cure rate.** Sixty-one children with 105 refluxing ureters had operation for correction of reflux. The initial operation successfully corrected the reflux in 88 of the 105 ureters (84 percent). Most of the 17 ureters in which reflux persisted after operation had been treated by the Hutch procedure initially. In 14 of the 17, the reflux was corrected by a second operation. The total cure rate, therefore, was 97 percent. Two patients (two ureters) refused further operation and one patient had unilateral nephrectomy. Grade I reflux occurred to

TABLE 1.—Management of Girls with Ureteral Reflux

| Treatment          | Patients | Ureters |
|--------------------|----------|---------|
| Operation .....    | 61       | 105     |
| No Operation ..... | 73       | 112     |
| TOTALS .....       | 134      | 217     |

TABLE 2.—Grade of Ureteral Reflux in Medically Treated and Surgically Treated Children with Urinary Tract Infection

| Grade of Reflux | Medical Group<br>(Number of Ureters) | Surgical Group<br>(Number of Ureters) |
|-----------------|--------------------------------------|---------------------------------------|
| 1 .....         | 44                                   | 12                                    |
| 2 .....         | 60                                   | 46                                    |
| 3 .....         | 8                                    | 47                                    |
| TOTALS .....    | 112<br>(73 patients)                 | 105<br>(61 patients)                  |

a minor degree in two contralateral ureters after operation.

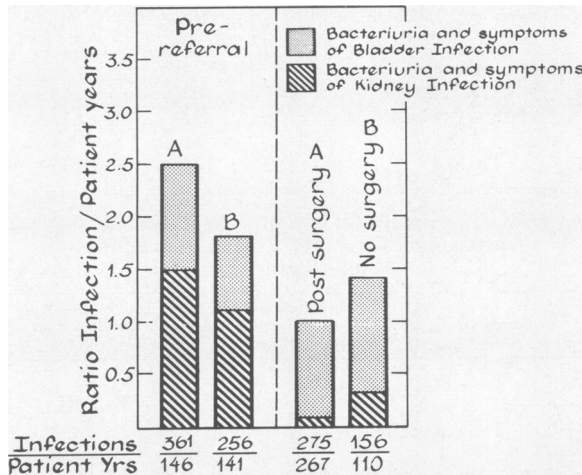
**Complications.** Ureteral obstruction occurred in eight ureters (six children); in six of these ureters (four children) the obstruction was corrected by ureteral re-anastomosis while in two ureters (two children) there was low grade obstruction which did not require operation. Interestingly, delayed ureteral obstruction occurred in one ureter 30 months following a successful reimplantation. In that case, an excretory urogram appeared normal 12 months after operation. Obstruction in the other seven ureters (five children) was apparent soon after operation. Six ureters became obstructed following the Politano-Leadbetter method of reimplantation. One patient presented with bilateral ureteral obstruction following a Paquin procedure done elsewhere.

**Infection results.** Urine culture data were studied in all the 134 children with reflux; 61 children had surgical correction of reflux, and 73 were treated medically. We compared the infection data in the two groups of children in reference to the following:

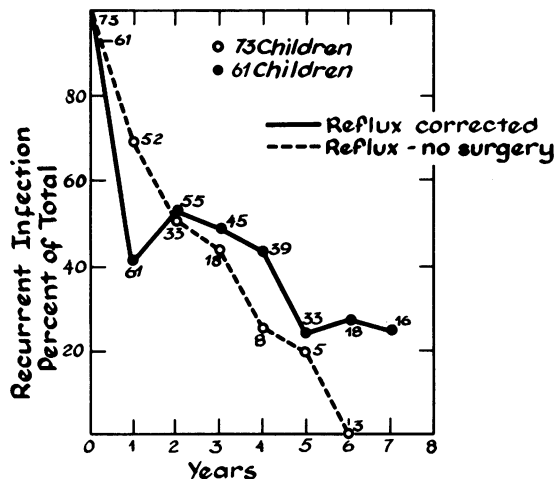
- The infection rate before referral to Stanford.
- The infection rate after corrective operation or medical therapy.
- The incidence of clinical pyelonephritis before referral to Stanford compared with the rate after operation or medical treatment.

Chart 1 indicates the rate and type of infection, measured in infections per patient year, in the two groups of children: (a) before Stanford referral, (b) either following surgical correction of reflux (surgical group) or after continuing medical care

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**Chart 1.**—Illustrates the infections per patient year in the two groups of children pre-referral and post-referral. Group A, reflux and surgically treated group—61 patients. Group B, medically treated group—73 patients.



**Chart 2.**—Annual incidence of infection in two groups of children after surgical correction of reflux (61 children) or after medical follow-up without surgery (73 children).

(medical group). The infection rates were similar in both groups of children before referral. After surgical cure of reflux, the infection rates did not differ significantly. Most importantly, the incidence of clinical pyelonephritis was greater than 50 percent of all infections before referral, but was reduced to 10 percent of the total infections in the surgical group and to less than 20 percent of the infections in the group followed medically.

As shown in Chart 2, of the 73 children with reflux treated medically, 52 were followed for at least one year and 33 for at least two years. Similarly, of the 61 surgically treated children all were followed for at least one year and 55 for two years.

The percentage of each follow-up group experiencing recurrent infections in any given year was similar in both groups. Indeed, at a point two years after surgical correction or medical care, more than 50 percent of both the medically and surgically treated children still experienced infections.

Chart 3 gives data on the infections in a child with reflux who experienced her first infection at age four and a half years and who was followed until age 15—eight and a half years after successful left ureteroplasty at age six and a half. This case history clearly indicates the infection incidence and severe morbidity before operation, followed by persistence of recurrent lower urinary tract infections for two and a half years after the procedure. Significantly, there was not a single episode of clinical pyelonephritis after surgical correction of reflux, despite the multiple episodes of bacteriuria which persisted during the initial postoperative period of two and a half years.

### Radiological Examinations

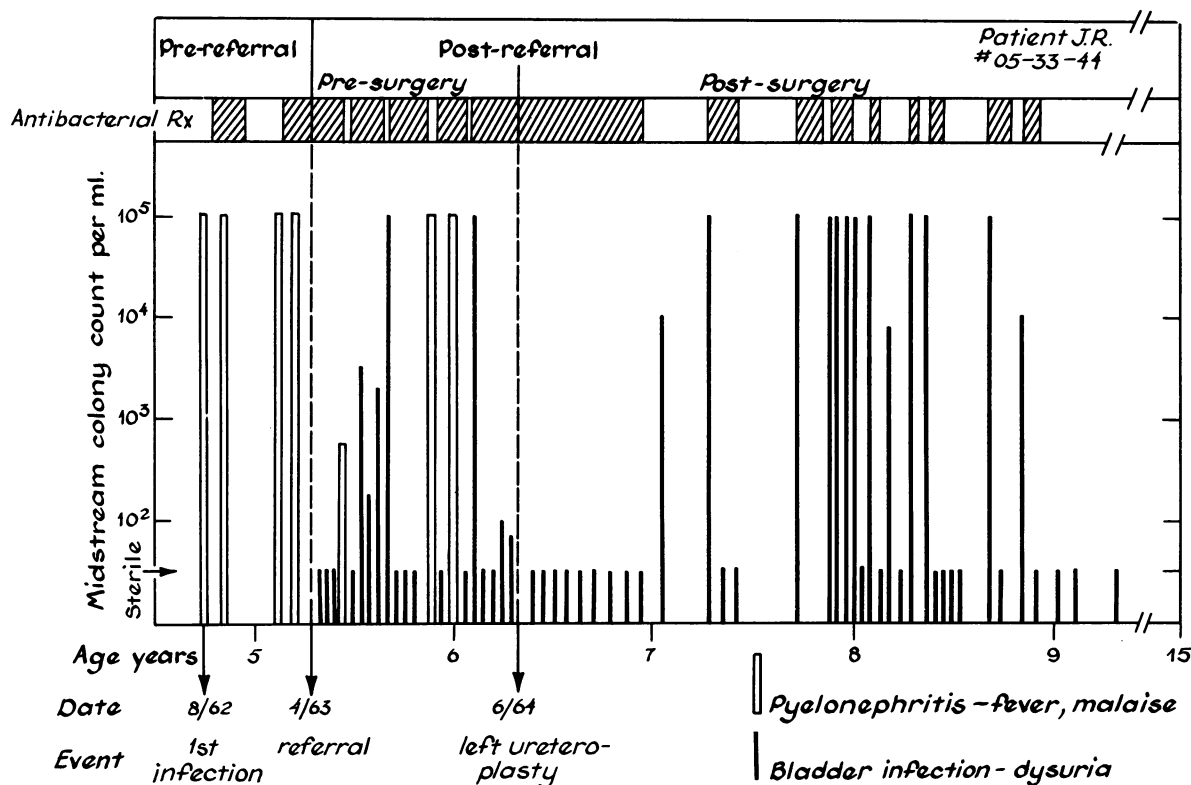
The results of the x-ray studies on these children will be presented relative to the following:

- Fate of refluxing renal units treated medically.
- Fate of refluxing renal units treated surgically.
- Relationship of renal clubbing and scarring to grade of ureteral reflux in children treated medically.

*Fate of refluxing renal units treated medically.* We were able to assess accurately the roentgen features in 110 refluxing renal units at a time not less than one year after the first recorded urinary infection. Forty-eight of these renal units were normal and 62 were clubbed and scarred. The higher the grade of reflux, the higher the observed incidence of clubbing and scarring (Tables 3 and 4).<sup>4</sup>

Multiple roentgen studies of 40 renal units were done over a period of at least two years. Sixteen of the 40 units were initially normal and 14 of these 16 were still normal at the end of the study. Twenty-four of the 40 units were clubbed and scarred when first assessed. In follow-up films nine showed no progression of clubbing and scarring while 15 showed evidence of deterioration. Specific case studies indicated that the infection control in the 15 patients whose kidneys deteriorated further was inadequate. All these patients had multiple episodes of clinical pyelonephritis.

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**Chart 3.**—Documented infection history of a child followed from age 4½ to 15 years, pre-referral, pre-operation and post-operation. Left ureteroplasty was performed at age 6½.

**Fate of refluxing renal units treated surgically.** Sixty-one children with 105 refluxing renal units had corrective operations (Table 1). We were able to analyze 37 renal units which were followed roentgenologically with multiple examinations for longer than one year postoperatively.<sup>4</sup> Thirteen were normal (35 percent) at time of operation and all remained normal afterward. Twenty-four of the 37 renal units (65 percent) showed clubbing and scarring before operation, and after operation eight showed no progression of renal changes, while 16 deteriorated further. It is important to state that in 13 of these 16 renal units, an acute episode of clinical pyelonephritis occurred just before corrective operation and the scar appeared within two years postoperatively; in three of the 16, a similar pyelonephritic episode occurred after ureteroplasty and the clubbing and scarring progressed within two years after the episode.

**Relationship of clubbing and scarring to grade of reflux in children treated medically.** In 20 of 26 normal renal units the reflux was grade I, while the reflux was grade III in 36 of 47 renal units with clubbing and scarring (Table 4).<sup>4</sup>

It should be reemphasized that after surgical

correction of reflux, no previously normal kidney showed deterioration and that 8 of 24 kidneys which were clubbed and scarred at the time of operation showed no deterioration after operation. Furthermore, all 16 renal units in which clubbing and scarring progressed after operation were in children who had had an episode of clinical pyelonephritis just before the procedure.

## Discussion

This article attempts to study the significance of ureteral reflux as it relates to the occurrence of urinary tract infection in girls. Some conclusions can be drawn regarding several pertinent questions.

- *What is the natural history of urinary tract infection in girls with ureteral reflux? And does surgical correction of reflux alter the infection pattern and influence the re-infection rate in these children?*


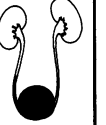
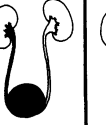



The results presented in this article and the first article in this series<sup>7</sup> clearly show that the infection rate in children with ureteral reflux who receive only medical therapy is similar to the rate in children without reflux. Before the time of re-

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TABLE 3.—*Refluxing Kidneys Treated Medically (From Filly R, Friedland GW, Govan DE, et al<sup>6</sup>)*

| Renal Morphology                  | Right | Left | Total |
|-----------------------------------|-------|------|-------|
| Clubbed and Scarred . . . . .     | 33    | 29   | 62    |
| Normal . . . . .                  | 18    | 30   | 48    |
| Total Refluxing Kidneys . . . . . | 51    | 59   | 110   |

TABLE 4.—*Relationship Between the Grade of Reflux and Presence or Absence of Clubbing and Scarring (From Filly R, Friedland GW, Govan DE, et al<sup>6</sup>)*

|  |  |  |  |  |
|--|---|---|---|---|
| STATE OF KIDNEY  | 0   | I   | II  | III   |
| <br>NORMAL              | 97  | 20  | 17  | 11  |
| <br>CLUBBED AND SCARRED | 3   | 6   | 17  | 36  |
| UNGRADED REFLUXERS (3)   |   |   |   |   |

ferral to our institution, more than 50 percent of infections in children with reflux were associated with fever and flank pain during an infection—quite in contrast to the benign type of clinical infection experienced by children without reflux.<sup>7</sup> In the group with reflux, the severity of infections lessened under good medical management, the incidence of clinical pyelonephritis decreasing to less than 20 percent of all infections. This compares favorably to an incidence of 10 percent in the group of children who had reflux.<sup>7</sup> Winberg et al<sup>8</sup> also found that when infections were well controlled in children with reflux, the incidence of clinical pyelonephritis was similar to that occurring in children who did not have reflux.

Analysis of our 61 children with reflux who had corrective operation and 73 children with reflux who were treated medically points up several facts. First, the incidence of infection in the pre-referral (Chart 1) period was slightly greater in the group of children who ultimately had operation, and the incidence of pyelonephritis was similar in both groups. Second, following either correction of reflux or close medical supervision the incidence of infection decreased. The annual incidence of infection in both groups was still over 50 percent two years after referral (Chart 2). Significantly, however, following anti-reflux operation the incidence of clinical pyelonephritis decreased from 50 percent of infections before to 10 percent of in-

fections after operation. This postoperative incidence of clinical pyelonephritis is identical to that found in a group of children without reflux.<sup>7</sup>

The annual recurrence rate of infection following treatment for both groups of patients is similar (Chart 2). In other words, surgical cure of reflux offers no greater protection from recurrence of infection than medical care alone. In addition, 21 of 61 patients in the surgical group and 11 of 42 patients in the medical group have had no further infection. These differences are not statistically significant.

Because of the similarities between the infection rates in our two groups of children following treatment, we plotted their respective drop-out rate from the infection pool after each successful treatment, against the drop-out rate of the children without reflux who were discussed in the first paper<sup>7</sup> and the theoretical 20 percent extraction rate described by Kunin.<sup>9</sup> Quite significantly the drop-out rates following each successful treatment of an infection were similar for the three groups of children with or without reflux and with or without surgical correction, and paralleled the theoretical 20 percent extraction rate. These data are clearly suggestive that reflux by itself is *not* the influencing factor in the recurrence rate of infection.

In summary of this section, several points need reemphasis: (1) that infections are not totally eradicated following correction of reflux, (2) that the rate of infection in surgically treated and in medically treated patients with reflux is similar, (3) that the incidence of clinical pyelonephritis is similar following surgical or medical treatment, and (4) that the drop-out rate from the infection pool is similar when one compares the surgically treated and the medically treated groups of children who had reflux with the children who did not.

• *Is the persistence of ureteral reflux deleterious to renal morphology and function in the sterile or infected state?*

Our data suggest that reflux, in the presence of infection, is deleterious to renal morphology as judged by renal clubbing and scarring, and that the incidence of clubbing and scarring is highest in association with the higher grades of reflux (Table 4).<sup>4</sup> Unfortunately, our first examination of most of our infected children with reflux did not take place until after the age of two years—few under the age of one year. Hence we did not know the state of ureteral reflux at birth or at the

time of the child's first infection. If it is true that there is a general improvement in the degree of reflux with increasing age of the patient,<sup>10</sup> then the renal units with scarring and low grades of reflux may well have had higher grades of reflux at an earlier age, as suggested by Rolleston et al.<sup>11</sup> Our study also substantiates Rolleston's data that the majority of renal scars occur in the renal units with grade III reflux. Other investigators have found a comparably high incidence of clubbing and scarring in refluxing renal units.<sup>12-14</sup> It is important to state, however, that all of the above observers were studying patients with reflux in the presence of infection. No evidence exists that reflux alone in the absence of infection will lead to functional renal changes.<sup>15,16</sup>

### *Current Thoughts on Treatment*

The general aim of treatment is to sterilize the urine, rid the patient of the annoying symptoms of infection, and prevent renal damage. Our studies strongly suggest that reflux has little influence on the initiation or recurrence of infection because:

- The drop-out rate from the infection pool is similar in children with reflux (surgically or medically treated) and children who do not have reflux.
- The recurrence rates of infection are similar whether correction of reflux was by surgical or medical management.

The incidence of reflux is measurably higher in children with urinary tract infection.<sup>10,17</sup> Numerous investigators have proved, however, that reflux has a tendency to improve or disappear with control of infection, or as the patient get older.<sup>10-13,18-23</sup> Smellie<sup>10</sup> showed that all forms of reflux in children tend to improve in time when the urine is kept sterile.

Additionally, ureteral reflux is rare in infants and older children without urinary tract infection.<sup>24-26</sup> By contrast, among children with infected urine at the time cystogram is done, 45 percent will show reflux.<sup>18</sup>

In a recent communication, Rolleston et al<sup>27</sup> discussed several instances of "intra-renal" reflux in infants under four years of age who had gross ureteral reflux. Renal scarring developed later in the areas of previous intra-renal reflux and, interestingly, scarring did not develop in areas of the same kidney not involved with the intra-renal reflux. These investigators suggested that renal scars might develop in this way in the newborn or infant kidney in the grossly refluxing state even

without infection, and conceivably might account for a majority of renal scars apparent in children who first come to the attention of the pediatrician or urologist at age two or three, already with severe renal damage. Has this apparent damage been present since birth and due to primary dysplasia? Has the damage been due to sterile gross reflux and only in areas of intra-renal reflux, or have both possibilities been augmented by the presence of infection? When one combines the above suggestions with the known fact that ureteral reflux seems to improve in time and disappear in a large number of instances,<sup>11,13</sup> it is highly suggestive that when we see a scar in a kidney of a child of three years, with minimal reflux, we may speculate that the reflux was gross at an earlier age, and possibly with an intra-renal component, with or without infections. Our radiological studies<sup>4</sup> have shown that morphologically normal kidneys become clubbed and scarred and that normal areas in otherwise damaged kidneys can become clubbed and scarred. These data suggest that the clubbing and scarring is probably secondary to reflux and infection rather than due to primary renal dysplasia. In experiments in pigs in which he obstructed the urethra and created reflux, Hodson showed focal clubbing and scarring in areas of intra-renal reflux.<sup>28</sup> None of the children in our series, however, had urethral obstruction.

What, then, is the purpose of stopping ureteral reflux? Our studies illustrate that poor infection control in a child with reflux leads to renal clubbing and scarring. Two-thirds of renal units in both the medical and surgical groups that we were able to study with multiple radiological examinations for more than one year showed progressive renal deterioration. In each instance the deterioration seemed to be related to a specific acute clinical pyelonephritic episode months earlier. Moreover, these radiological studies<sup>4</sup> suggested that further scarring of a renal unit took up to 24 months to appear after an infective insult. We would like to be able to say that corrective surgical operation "protected" the renal unit from damage. Our data, however, do not seem to bear this out, unless, of course, we blame the continuing renal deterioration on the infections that occurred before operation. Such seemed to be the case in 13 of 16 renal units in our surgical group in which there was further deterioration after operation.

We feel that the progression of clubbing and

scarring in two-thirds of the renal units in our medically treated group can be blamed on the fact that we used a specific, intermittent ten-day program of drug therapy. Although such treatment effectively eradicated the infection, it did not guarantee protection from the next infection. As a consequence, the child was left "exposed" to possible further renal infection and renal damage.

These data contrast sharply with the absence of progression of renal damage in children (Smellie<sup>10</sup>) for whom continuous antimicrobial therapy was prescribed, generally for the duration of the reflux. In her group of 34 refluxing children treated medically over a period of one to nine years, 26 when first examined had normal kidneys; in 24 of the children the kidneys remained normal and two patients showed slow renal growth. Eight children initially had scarred kidneys and in follow-up two had normal renal growth, two slow growth and four none. Fresh scarring developed in only one neonate following an acute infection.

If reflux is allowed to persist, therefore, the renal unit must be protected from infection. As we shall discuss shortly, we strongly advise initial sterilization of the urinary tract followed by long-term preventive medication for children who have shown a proclivity to frequent bacteriuric episodes.

#### *Current Treatment Regimen*

Screening of large numbers of children<sup>17,28,29</sup> has identified those who are bacteriuric with urinary tract abnormalities.<sup>17,29,30</sup> In a recent survey of 8,722 school children five to eleven years of age, Asscher et al<sup>29</sup> found a 1.7 percent incidence of bacteriuria; in this infected group 23 percent had reflux and 17 percent had renal scarring. Such surveys have helped to identify the high incidence of renal disease which seems to exist in the asymptomatic infected population and have alerted clinicians to the need for earlier radiological studies in children who are infected. At the moment it seems important to identify children with urinary tract infection as early as possible. Heale et al<sup>31</sup> indicated that one cannot always predict the presence of infection on symptoms alone. Indeed, Heale found that only 9.1 percent of 789 children presenting at a general pediatric clinic with either specific symptoms such as frequency, dysuria and loin pain, or with non-localizing symptoms such as fever, lethargy and abdominal pain, were actually infected. Infection was present in 14.3 percent of children with spe-

cific symptoms, but in only 4.4 percent with non-localizing symptoms.

Heale<sup>32</sup> subsequently showed that 33 percent of these infected children have either ureteral reflux or a renal scar or both. We should therefore identify the child with symptomatic infection and then investigate further to determine the risk. With that done and the patient treated and evaluated radiologically, one is in a position to outline a program of continuing care.

*Treatment of the infection.* The presence or absence of reflux does not influence our treatment of an infection. One should treat all infections with a drug most appropriate for the organism involved. Most recurrences of infection are new infections and not a relapse of an old infection.<sup>33</sup> Therefore, we recommend a follow-up urine culture while the child is receiving a ten-day course of antibiotic therapy and again four to seven days after cessation of treatment. Only by this method can we distinguish between relapse and re-infection. If the urine does not become sterile, it may be because of one or more of the following: Use of the wrong antibacterial agent; a new infection; presence of a foreign body such as a calculus; diminished renal function—inadequate to concentrate the antibiotic; or obstruction. In general, however, intelligent use of antimicrobial agents should sterilize the urine.

If a child has frequent infections despite good care, we initially sterilize the urine with specific antimicrobial medication for ten days and then prescribe long-term preventive therapy with nitrofurantoin taken morning and evening or evening only. This regimen is continued for at least six months and then stopped for a trial period as there is always the chance that the patient will drop out of the infected group. If further infection develops, drug therapy is resumed as before. This form of management, used during the latter half of our study, proved to be highly successful, and although our prospective study of results is not yet sufficiently long or involving appropriate numbers of patients, we are encouraged to feel that the control of infections will be as good as reported elsewhere.<sup>13</sup>

*Treatment of the reflux.* Infection control is paramount in a child with reflux. We adhere to the policy just outlined. If infection cannot be adequately controlled thereby, in our opinion surgical correction is required. Even though our data would suggest a continuing infection pattern in the first two years after operation, in about 50 per-

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cent of the children in our series the incidence of clinical pyelonephritis was dramatically reduced.

It is to be hoped that surgical intervention would not be required in a child with grade I or II reflux, for in a majority of cases the reflux will abate with time, as was discussed earlier. In grade III (gross) reflux, one must give consideration to anti-reflux operation even though infection may be quite well controlled, particularly in the younger age group (newborns and infants), on the basis of the discussion already presented.<sup>27</sup>

We strongly oppose the idea of surgical correction of reflux simply because reflux is present. Factors such as age, sex, degree of reflux, infection control, and reliability of the parents of the child must be considered in deciding whether or not to operate. We believe surgical correction of reflux can be justified only on the basis that it will preserve renal function. Good infection control with antimicrobial agents is our recommended treatment; but if control cannot be achieved thereby, then we suggest operative intervention.

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